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Scholkmann, Felix

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# Two emerging topics regarding long-range physical signaling in neurosystems: Membrane nanotubes and electromagnetic fields

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**Abstract:** In this review paper, an overview is given of two emerging research topics that address the importance of long-range physical signaling in living biosystems. The first topic concerns the biophysical principles and the physiological significance of long-range cell-to-cell signaling through electrical signals facilitated by membrane nanotubes (MNTs) (also called “tunneling nanotubes”), namely long membrane extensions that connect cells, discovered about 10 years ago. This review paper looks at experimental results that showed electrical signals being propagated through MNTs, and that MNT-mediated electrical coupling between brain cells involves activation of low-voltage-gated calcium channels. The significance of electrical cell-to-cell coupling through MNT for neuronal communication is discussed. The second topic deals with endogenous electromagnetic fields generated by nerve cells. The review concludes that these fields are not just an “epiphenomenon” but play a fundamental role in neuronal processes. For example, electromagnetic fields from brain cells feed back to their generating cells and to other cells (ephaptic coupling) and, for example, modulate the spiking timing of them. It is also discussed that cell membranes of neurons have specific resonance properties which possibly determine the impact of endogenous electric field fluctuations with respect to field strength and frequency. In addition, it is reviewed how traveling and standing waves of the endogenous electromagnetic field produced by neuronal and non-neuronal cells may play an integral part in global neuronal network dynamics. Finally, an outlook is given on which research questions should be addressed in the future regarding these two topics.

**Keywords:** Neural signaling; long-range physical cell-to-cell interactions; membrane nanotubes; ephaptic coupling; endogenous electromagnetic fields.

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## 1. Introduction

How is information transfer mediated in the central nervous system, specifically in the brain? There exist 75–125 billion neurons in the human brain (Lent *et al.*, 2012) – how do they communicate to facilitate complex cognitive processes? The scientific journey to answer this question can be traced back at least to the 19<sup>th</sup> century when, in the 1870s, Caton observed “electrical currents of the brain” (Caton, 1875). In the 1890s, Cajal realized that neurons conduct and receive electrical impulses along their axons as well as receive impulses via dendrites (De Carlos and Borrell, 2007), and Sherrington discovered in the 1890s the fundamental role of synapses for neuronal impulse transmission (Pearce, 2004). More than a half century later, it was increasingly recognized that synaptic transmission is not the only signaling mode: the discovery of direct signal connections between brain cells via gap junctions in the 1970s (e.g., Sloper, 1972; Sotelo and Llinás, 1972; Sloper and Powell, 1978) and via extrasynaptic chemical volume transmission (i.e. short range and long range chemical signaling) in the 1980s (e.g., Agnati *et al.*, 1986; Agnati *et al.*, 1987; Fuxe *et al.*, 1988a, 1988b) extended our understanding of how the cells in our brain communicate with each other. In parallel, the insight in the 1960s that neurons form structural and functional networks (“neuronal networks”) (e.g., Greene, 1962a, 1962b; Uttley, 1966; Kennedy *et al.*, 1969) brought new insights and triggered the emergence of new research fields, e.g., neuroinformatics and artificial intelligence.

However, our understanding of how the brain works is still in its infancy. Major research projects have been initiated in recent years to speed up progress in neuroscience (e.g., “Blue Brain Project” (Markram, 2006), “Human Brain

Project” (Markram, 2012), “BRAIN initiative” (Alivisatos *et al.*, 2012). But will these ambitious projects succeed in offering breakthrough insights into how brains work? A growing number of critical voices are being raised that point out weaknesses in the projects (Eliasmith and Trujillo, 2014; Grillner, 2014; Poo, 2014). In my view, the greatest challenge is to incorporate novel approaches and concepts into the research goals that have recently been getting more and more attention. Such novel concepts were, for example, the insight that i) non-neuronal cells (i.e., glial cells) have a larger significance than previously thought for neuronal processes (Clarke and Barres, 2013), that ii) the cooperative phenomena of brain dynamics emerges as a consequence of the brains dynamical criticality involving phase transitions (Haimovici *et al.*, 2013; Alonso *et al.*, 2014; Plenz and Niebur, 2014) and metastability (Tognoli and Kelso, 2014), iii) information processing in and by axons (Pinault, 1995; Debanne, 2004), microtubuli (Hameroff, 2013; Sahu *et al.*, 2013a, 2013b) and dendrites (Das and Narayanan, 2014; O'Donnell and Nolan, 2014), or – most importantly from my point of view – that (iv) there exist newly discovered cell-to-cell communication channels and processes that may play a fundamental role in functional brain activity.

As early as the late 1980s, Agnati and Fuxe had come to the conclusion that there are two basic signal transmission modes in the brain: wiring transmission (WT) and volume transmission (VT) (Agnati *et al.*, 1986; Agnati *et al.*, 1987; Fuxe *et al.*, 1988a, 1988b). Whereas WT refers to all signaling modes that involve a direct chemical or physical cell-to-cell connection (e.g., synaptic transmission and information transfer via gap junctions), VT subsumes all chemical and physical modes that take place within the extracellular space (e.g., diffusion of transmitters, propaga-

tion of currents and electromagnetic fields). VT is also known as “nonsynaptic diffusion neurotransmission” (Bach-Y-Rita, 1993, 1995, 2004; Kercel, 2004). In a recently published paper, Agnati *et al.* (2014) highlighted that two newly discovered signal transmission types in the brain seem to be of significant importance to further understand the function of the brain: signaling via (i) *membrane nanotubes* (a new form of WT), and (ii) via *extracellular vesicles* (a new form of VT). Agnati *et al.* conclude that “their importance in integrative actions is potentially enormous” (Agnati *et al.*, 2014). In parallel, more and more research is showing that *endogenous electromagnetic fields* play a fundamental role, and it is concluded that “endogenous brain activity can causally affect neural function through field effects under physiological conditions” (Anastassiou *et al.*, 2011).

The aim of the present review article is to give a concise overview of the neurobiological significance of neural signaling via electrical signal transmission by membrane nanotubes and information transfer by endogenous electromagnetic fields since both of these transmission modes allow long-range signaling which opens up new possibilities to describe and understand large-scale neurobiological processes happening in the brain.

## 2. Electrical Signaling via Membrane Nanotubes

### 2.1 The 2004 discovery

In a seminal paper published in *Science* in 2004, the research group of H.-H. Gerdes reported the discovery of a “novel biological principle of cell-to-cell interaction based on membrane continuity” (Rustom *et al.*, 2004): connections between different types of cells (rat pheochromocytoma (PC12), human embryonic kidney (HEK), normal rat kidney (NRK) cells) of 50–200 nm in diameter and a several cell diameters in length. These structures, originally termed “tunneling nanotubes” but later also called “membrane nanotubes” (MNT) by many authors, are dynamic protrusions from cell surfaces filled with cytoplasm, having a lipid bilayer and containing actin, mitochondria or/and microtubules to varying degrees (depending on the specific type of MNT-based cell-to-cell connection), i.e., MNTs exhibit a diverse morphology and structural composition (Austefjord *et al.*, 2014). Whereas this first detection of MNTs was performed in an *in vitro* study, the evidence that MNTs also exist *in vivo* was first supplied in 2008 by Chinnery *et al.* (2008) who observed MNTs between dendritic cells within the mouse cornea. Up to now, numerous studies showed that MNTs can facilitate the intercellular transport of a great variety of signaling carriers (e.g.,  $\text{Ca}^{2+}$ , caspase-3), organelles (e.g., mitochondria, membrane components, lysosomes, endosomes, Golgi complex, endoplasmic reticulum) of bacteria and viruses (see for review Marzo *et al.*, 2012; Zhang and Zhang, 2013).

### 2.2 MNTs in the brain: What is their neurobiological significance?

Regarding the significance of MNTs for the biophysical basics of neuronal activity, several new discoveries provided new and significant insights into this topic, whereas the works of Wang *et al.* are of particular importance.

Taking into account the hint that artificial MNTs are a good conductor for electrical currents (Tokarz *et al.*, 2005), Wang *et al.* investigated with *in vitro* experiments if MNTs between different cell types exhibit the same behavior, i.e., *electrical coupling*. The results, published in 2010 (Wang *et*

*al.*, 2010), showed that long-distance electrical coupling can indeed happen between human embryonic kidney (HEK293) cells, human umbilical vein endothelial cells (HUVECs), NRK cells and quail neuronal crest (NCC) cells. Not all individual cells of these types showed this electrical coupling, however. No electrical coupling at all could be measured for PC12 cells. The electrical coupling was observed as a spread of depolarization from a mechanically stimulated cell to another cell connected by a MNT. It was shown that the depolarization of the connected cell activates low-threshold voltage-gated  $\text{Ca}^{2+}$  channels then causing an increase in intracellular  $\text{Ca}^{2+}$  levels ( $[\text{Ca}^{2+}]_i$ ). The average electrical conductance of cells connected via MNTs and showing electrical coupling was measured to be  $566 \pm 129$  pS (for comparison, the conductance via gap junction is estimated for NRK cells to be in the range of 30–300  $\mu\text{S}$ , Bathany *et al.*, 2012). After careful experiments the authors proposed a solution to explain the observation that not all HEK292, HUVEC, NRK and NCC cell showed electrical coupling and PC12 did not show it at all: from these cells, PC12 did not express gap junctions whereas HEK292, HUVEC, NRK and NCC cells express the gap junction protein connexin 43 (Cx43), also known as gap junction alpha-1 protein (GJA1) – a compound of a gap junction. Thus, the authors concluded that “TNT-mediated electrical signals are transmitted through gap junctions at a membrane interface between the TNT and one cell of the connected pair” and that “the transfer of electrical signals via TNTs and the subsequent activation of physiologically relevant biophysical signals may provide a unique mechanism for long-distance cellular signaling” (Wang *et al.*, 2010).

But does this MNT-mediated electrical coupling also happen between brain cells? This question was answered in the affirmative sense by Wang *et al.* who published 2012 experimental proofs of electrical coupling by MNTs between immature hippocampal *neurons* and adult *astrocytes* (expressing Cx43) (Wang *et al.*, 2012). Regarding the significance of this discovery, Wang & Gerdes concluded that “given the wide distribution of TNTs across cell types, it is interesting to speculate that the presence of TNTs in brain could add an additional level of complexity to information processing. In particular the passive flow of small electrical currents between different neurons, or different branches of their dendritic trees, or even between neurons and astrocytes could provide instructive communication cues” (Wang and Gerdes, 2012). Interestingly, there is similarity between MNTs and axons/dendrites: Wang *et al.* (2010) discovered that microtubules were present in all detected MNTs between neurons and astrocytes, similar to the situation in axons and dendrites which also contain microtubules.

In conclusion, evidence is accumulating that MNTs could play a role in long-range electrical neuronal communication in the brain. Future research needs to investigate whether this kind of coupling also happens between different configurations of neuronal and non-neuronal cells. Electrical signaling via MNTs, as a new form of wiring transmission, could add a new layer of complexity to the function of complex cell networks (e.g., neuronal networks and astroglial networks) in the brain.

## 3. Endogenous Electromagnetic Fields and their Role for Brain Activity

### 3.1 Ephaptic coupling: Field-mediated signaling between cells

More and more evidence is accumulating to support the notion that there is a fundamentally important volume transmission mode between brain cells: cell-to-cell signaling via electromagnetic fields, termed *ephaptic coupling*.<sup>1</sup> Whereas several previous studies concluded that there exists a fast, VT-based, signaling between neurons, not based on synapses or gap junctions (Arvanitaki, 1942; Ramon and Moore, 1978; Rasminsky, 1980; Blumberg and Jänig, 1982; Richardson *et al.*, 1984; Traub *et al.*, 1985; Yim *et al.*, 1986; Jefferys, 1995; Dudek *et al.*, 1998; Holt and Koch, 1999; Costalat and Chauvet, 2008), the work published a few years ago by Anastassiou *et al.* (2010, 2011), Ozen *et al.* (2010) and Fröhlich & McCormick (2010) picked up on this topic and initiated a novel interest in ephaptic coupling of brain cells – especially regarding its relevance for neurobiological processes in our brain.

Using computational modeling, Anastassiou *et al.* (2010) showed that a time-varying endogenous extracellular electric field  $\mathbf{E}$  (i.e., the negative gradient of the extracellular potential  $\phi_e$ ,  $\mathbf{E} = -\nabla\phi_e$ ) influences the spike timing of adjacent neurons. This *in silico* finding was replicated in a subsequent *in vitro* study which clearly demonstrated that “extracellular fields feed back onto the electric potential across the neuronal membrane via ephaptic coupling” (Anastassiou *et al.*, 2011). In particular it could be proven that an endogenously produced field  $\mathbf{E}$  can affect the behavior of neurons principally in two ways depending on the membrane potential ( $\phi_m$ ) of the cell that “receives” the time-varying (oscillating) field. On the one hand, if  $\phi_m$  is in the *subthreshold regime* (i.e. when the neuron is not spiking) then the field also causes changes in  $\phi_m$  (and in the potential of the intracellular space,  $\phi_i$ , too) with the same frequency; on the other hand, if the neuron is *spiking*, the field causes phase changes in the spiking dynamics (phase locking of spikes to the external field). Thus, an extracellular field can cause an entrainment of  $\phi_m$  (membrane potential fluctuation entrainment) or the spiking activity (spike entrainment), depending on  $\phi_m$ . Anastassiou *et al.* concluded that “endogenous brain activity can causally affect neural function through field effects under physiological conditions” (Anastassiou *et al.*, 2011).

Further properties of ephaptic coupling were observed by Fröhlich and McCormick (2010). Using *in vitro* experiments with slices of ferret visual cortex they showed that the effect on neighboring cells is different depending on the endogenous  $\mathbf{E}$  field characteristic. Whereas a *constant*  $\mathbf{E}$  field can directly cause changes in  $\phi_m$  (e.g.,  $\mathbf{E} = 4 \text{ mV/mm} \rightarrow \Delta\phi_m \approx 1 \text{ mV}$ ) and also an increase in the frequency of spontaneous oscillations of  $\phi_m$ , a *time-varying*  $\mathbf{E}$  field induces spike entrainment (as also shown by Anastassiou *et al.*, 2011). Regarding the spike entrainment, Fröhlich and McCormick could also demonstrate that the specific *dynamics* of time-variation of  $\mathbf{E}$  matters: the spike entrainment effect was stronger when  $\mathbf{E}$  had a complex dynamic with irregular patterns compared to an  $\mathbf{E}$  field with a sine wave modulation. Since endogenously recorded  $\phi_e$  also exhibits this complex time-dependent behavior it can be assumed that the endogenous field characteristics are particularly suitable to cause ephaptic coupling between cells.

By using a different approach, i.e. applying an oscillating potential on the surface of the skull or the dura (i.e., the thick membrane that surrounds the brain) of anesthetized rats (transcranial electric stimulation, TES), Ozen *et al.* (2010) proved that the spike entrainment observed *in vitro* (Fröhlich and McCormick, 2010; Anastassiou *et al.*, 2011) takes also place *in vivo*.

## 3.2 The possible physical mechanism behind ephaptic coupling

In order to elucidate the physical principles enabling the long-range physical coupling of cells via field-effects, two basic factors have to be considered: the *generation* of the fields and the *reception* of them. In the following, a brief summary is given regarding these two aspects.

All sub-cellular (e.g., biomolecules, cell organelles), cellular, and supra-cellular (e.g., brain tissue, extracellular matrix, vessels, fluids) structures of the brain possess unique spatio-temporally varying electrical charge distributions which cause electromagnetic fields. In addition, moving charges and ions are part of every organization level of the brain. These resulting electrical potential changes can be measured directly (i) in the brain by intracranial electroencephalography (iEEG) (comprising a high-frequency part ( $> 500 \text{ Hz}$ ): multiunit activity (MUA), and a low-frequency one ( $< 500 \text{ Hz}$ ): local field potential (LFP)), (ii) on the cortical surface (electrocorticography (ECoG)), (iii) on the scalp (electroencephalography (EEG)), or (iv) directly from cells using, for example, microelectrodes.

For the ephaptic coupling of brain cells, the sum of all fields located in the extracellular space (i.e., the space outside the plasma membrane) is of relevance. As recently described in detail by Hales (Hales, 2014), the EM field facilitating ephaptic coupling between brain cells can be described as primarily caused by three processes: (i) the transmembrane potential of each cell induces a large electric field (in the order of  $10^6\text{--}10^7 \text{ V/m}$ ) (“background transmembrane electrostatic field”), (ii) activity of transmembrane ion-channels and the associated ion flows result in a dynamic electric fields  $\mathbf{E}$  and a magnetic fields  $\mathbf{B}$  located at the ion channels, as well as a dynamic transmembrane electric dipole field, and (iii) the inhomogeneous and changing distribution of ion channels on the cell membrane cause an inhomogeneity and slow change of the transmembrane field. The sum of these fields is then present in the extracellular space. From another point of view, the extracellular electromagnetic field surrounding the brain cells is formed by different neurophysiological processes (Buzsáki *et al.*, 2012; Reimann *et al.*, 2013), e.g., synaptic activity (i.e., extracellular dipole current flow from inhibitory to excitatory synapses), changes in  $\phi_m$  and transmembrane currents of neurons, sodium ( $\text{Na}^+$ ) and calcium ( $\text{Ca}^{2+}$ ) spikes/waves, spike after-hyperpolarizations, ionic/current movements between cells, and membrane potential changes of glial cells. In addition to these cellular sources other sources contribute to the extracellular EM field, i.e., current/ion movements in fluids (e.g., blood, lymph, cerebrospinal fluid, interstitial fluid), activity of brain microvascular smooth muscle and endothelial cells, and changes in the extracellular field potentials across the blood-brain (Tschirgi and Taylor, 1958; Held *et al.*, 1964; Caspers *et al.*, 1987; Revest *et al.*, 1993, 1994; Voipio *et al.*, 2002; Mycielska and Djamgoz, 2004; Tétrault *et al.*, 2008; Trivedi *et al.*, 2013).

Although classically described as *endogenous electric fields*, the above listing of these diverse processes involved in creating fields illustrates that a more correct and general term is *endogenous electromagnetic fields*, since the field mediating ephaptic coupling comprises electric and magnetic field components with time-varying field strengths on different time scales. This conclusion about the terminology used is supported by the recent work of Hales which showed that it is necessary to speak of the “brain’s endogenous electromagnetic field” in order to do justice to the complex time-varying electric and magnetic field components (Hales, 2014).

<sup>1</sup> The term “ephaptic” is derived from the Ancient Greek verb ἐφαπτο [éphapsis], meaning “touching”.

Having briefly discussed the processes that are involved in the generation of the brain's endogenous electromagnetic field, the question remains as to how the electromagnetic-field-mediated cell-to-cell coupling is generated? From a physical point of view such a coupling can be realized by the field effect of charges, described by the Lorentz law (Muehsam and Pilla, 2009; Hales, 2014), and possibly near-field induction effects, i.e., *electromagnetic induction* or *electrodynamic induction* facilitating wireless energy transmission. For electrodynamic induction (which is, regarding to the near-field condition, analogous to *evanescent-wave coupling* in optics), a resonance condition must be fulfilled. Interestingly, it is known that brain cells possess resonant properties, i.e., frequency-dependent excitability (Llinás, 1988; Pike *et al.*, 2004; Reinker *et al.*, 2004; Schreiber *et al.*, 2009; Tohidi and Nadim, 2009; Moca *et al.*, 2014) – a property that could play a role for the EM-field-mediated cell-to-cell coupling. This frequency preference of neurons due to the membrane potential resonance (MPR) is observed in many types of neurons, e.g., interneurons (“resonator interneurons”), thalamocortical neurons and pyramidal neurons (Moca *et al.*, 2014). Regarding MPR in the context of electromagnetic-field-mediated cell-to-cell coupling, two additional aspects may be of relevance: (i) Reinker *et al.* (2004) discovered that both, MPR and *stochastic resonance* (SR) are properties of neurons. The excitability and firing patterns of neurons depend on the *frequency* of the input signal (mediated by the MPR effect) and the *noise level* of the input signal (mediated by SR). This means that the frequency as well as the magnitude of spontaneous fluctuations of the endogenous electromagnetic field could possibly have an impact how the receiving cells react on it. (ii) That there exist two resonance and firing regimes in neurons was discovered by Schreiber *et al.* (2009). They showed that the optimal neuronal firing occurs when (a) the stimulus frequency equals the intrinsic firing rate of the cell (firing-rate resonance in the *mean-driven firing regime*), and when (b) the stimulus frequency equals the resonance properties of the subthreshold membrane potential (MPR in the *fluctuation-driven firing regime*). They concluded that their analysis “supports the view that neurons are endowed with selection mechanisms that allow only certain stimulus frequencies to induce reliable spiking. By modulating the intrinsic cell properties, the nervous system can thus tune individual neurons to pick out specific input frequency band with enhanced spike precision of spike probability” (Schreiber *et al.*, 2009).

Another interesting aspect is that the electromagnetic field characteristics of a neuron strongly depend on the spatial structure of the axons, dendrites and the position of the soma as shown in detail by the simulations conducted by Hales (2014). Also the orientation of the field with respect to the biological structure determines the coupling – for example, Chan and Nicholson (1986) demonstrated that the specific orientation of the dendrite with respect to the field determines if an applied electromagnetic field induces excitation or inhibition in neurons.

### 3.3 Ephaptic coupling: What is its neurobiological significance?

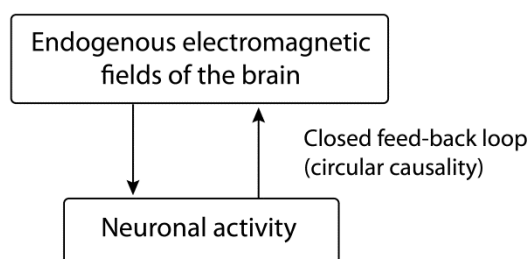
The classical view is that the brain's endogenous electromagnetic fields are just an *epiphenomenon*, i.e., they have no functional relevance. This view must be challenged according to the wide experimental evidence that is now available showing how brain cell interaction can be mediated by endogenous electromagnetic fields. As highlighted for example by Hales (2014), Anastassiou *et al.* (2011), Tiganj *et al.* (2014), and Fröhlich & McCormick (2010),

neuronal activity and the endogenous EM field of the brain constitute a *feedback loop* with *bidirectional causality* (see **Fig. 1** for a visualization). Taking into account the fact that the brain's endogenous EM field is an emergent phenomenon of the underlying physiological processes which then act in a top-down manner on these processes, the term *circular causality* (Haken, 1977) seems to be even more appropriate to describe this relationship.

Considering the brain's electromagnetic fields not as being an epiphenomenon but as an integral component of neurophysiology enables a novel way of describing spatio-temporal pattern of neuronal activity. Classically such global models of neuronal activity (“neural field theory”, “neural field equations”) do not consider electromagnetic field-mediated coupling effects between neurons but treat the neuronal activity in a field theoretical framework (e.g., Griffith, 1963, 1965; Wilson and Cowan, 1973; Coombes, 2005). The “field” concept in these models is usually considered as simply a mathematical framework modeling the neuronal activity patterns – an approach that is already powerful in describing large-scale neuronal activity. For example, modeling the long-range interaction between neurons over the whole brain via wave processes mediated by signal propagation in cortico-cortical fibers (e.g., Nunez and Srinivasan, 2006) enables an explanation of “field-mediated” phenomena like traveling waves and standing waves observed in different neurophysiological recordings (e.g. EEG). Such traveling waves have been observed in different frequency ranges and linked to different types of brain activity: e.g. traveling  $\alpha$  waves in human EEG signals (phase speed:  $6.5 \pm 0.9$  m/s, Patten *et al.*, 2012;  $3.6$ – $10.4$  m/s, Klimesch *et al.*, 2007;  $7$ – $11$  m/s, Burkitt *et al.*, 2000),  $\beta$  waves (phase speed:  $6.5 \pm 0.9$  m/s, Patten *et al.*, 2012),  $\gamma$  bursts ( $0.7$ – $2.1$  m/s, Bahramisharif *et al.*, 2013) or slow oscillations during sleep ( $1.2$ – $7.0$  m/s, Massimini *et al.*, 2004). That the global neuronal activity of the brain shows features of standing waves was for example, shown by Burkitt *et al.* (2000) and recently by Müller *et al.* (2014). Burkitt *et al.* demonstrated that “the spatial structure of a visual stimulus influences the emergence of travelling and standing waves within the cortex”, i.e., “central-field checkerboard pattern will preferentially drive travelling waves while a full-field flicker will drive standing waves” (Burkitt *et al.*, 2000). Müller *et al.* (2014) observed an EEG correlation pattern covering the whole brain during pre-seizure, seizure and post-seizure states. It was hypothesized that a field effect may be the cause triggering and orchestrating the spiking activity of single neurons as well as entire populations of neurons. Regarding the “nature” of the standing wave, the authors pointed out that according to their understanding it is “not an electromagnetic wave” but more a collective oscillatory phenomenon of neurons. This is in line with the classical neural field theoretical approach describing neuronal network activity as “embedded in global fields of synaptic action” (Nunez and Srinivasan, 2006). However, from this, the next logical step is to incorporate the brain's electromagnetic field into neural field modeling, i.e. assigning the field a real physical entity – something that has already been done. For example, Beim Graben and Rodrigues (2014) presented a model for the “microscopic coupling of continuous neural networks, i.e., neural fields, to the electromagnetic field” using the Amari equation (Amari, 1977).

In conclusion, ephaptic coupling of brain cells via the brain's electromagnetic fields could play a significant role in functional brain activity. The electromagnetic fields could possibly form a *global spatiotemporally varying interference pattern* that connects complex cell networks and functional modules of the brain, in addition to the other

WT and VT signaling modes. Another neurobiological function of the electromagnetic fields could also be rely in having an effect on dynamics of neurobiological structures, i.e. neuronal growth and neuronal migration (as already experimentally investigated; for a review see McCaig *et al.*, 2009). Also the electromagnetic fields may modulate the electrical cell-to-cell signaling process via gap junctions (Bennett and Zukin, 2004) by influencing the current flow, or the electromagnetic fields characteristic could be changed by the gap junction mediated coupling. In addition, the electrical coupling via membrane nanotubes could be affected by the field. Furthermore, biomolecules (neurotransmitters in particularly) could be influenced by the electromagnetic fields and could modulate the field properties in parallel. For example, the brain's electromagnetic fields may modulate the protein-ligand recognition which is recently described as an electromagnetic field effect (Alocci *et al.*, 2013), or the neurotransmitters could change the resonance properties of neurons, as already discussed by Silberstein *et al.* (1995). Finally, the physical process of synaptic transmission – which can be described as involving quantum mechanical tunneling (Walker, 1977) – might be influenced by the endogenous electromagnetic fields of the brain.



**Fig. 1:** Visualization of the interplay between neuronal activity and the endogenous electromagnetic fields of the brain.

#### 4. Summary, Conclusion and Outlook

In conclusion, this focused review article gives an introduction on two modes of cell-to-cell signaling that are most probably of fundamental significance in the spatiotemporal organization of brain activity: electrical signals transmission via membrane nanotubes, and ephaptic coupling between cells via electromagnetic fields. These two topics are expected to increasingly become the focus of neuroscientific research in the near future. This would not only facilitate our understanding of the biophysical principles governing brain function but also enable new approaches how to modulating brain activity through application of fields to the brain in an invasive or non-invasive manner. Such non-invasive techniques, like “transcranial direct current stimulation” (tDCS) (Nitsche *et al.*, 2008; Stagg and Nitsche, 2011; Zheng *et al.*, 2011; Kalu *et al.*, 2012), “transcranial alternating current stimulation” (tACS) (Chaieb *et al.*, 2011a; Ali *et al.*, 2013; Antal and Paulus, 2013; Herrmann *et al.*, 2013) and “transcranial random noise stimulation” (trNS) (Terney *et al.*, 2008; Chaieb *et al.*, 2011b; Laczó *et al.*, 2014) are already getting more and more attention in the field of neuroscientific research. Another aspect where new insights into electrical and electromagnetically cell-to-cell coupling in the brain could have an impact is the research about the effect of external electromagnetic fields (caused by technical devices such as cell phones) on neurophysiological processes. Non-thermal effects not yet understood (e.g., Bawin *et al.*, 1973; Huber *et al.*, 2002; Sinha *et al.*, 2008; Schmid *et al.*, 2012; Mohammed *et al.*, 2013) could possibly be explained by considering the electrical

and endogenous electromagnetic processes in brains. Finally, the inclusion of the novel cell-to-cell communication modes in models about cognitive processes, and ultimately about consciousness, could lead to new insights. The electromagnetic theories of consciousness and mind developed so far (e.g., McFadden, 2002a, 2002b; Pockett, 2012; Mostyn, 2013) will benefit from new basic research onto electrical and electromagnetic processes in the brain, and they could also offer new hypotheses to be tested that link the brain's electrical and electromagnetic processes to subjective experience and cognitive processes.

Further aspects for future research related to the topics discussed in this review paper would be, for example, investigating the link between the discussed electrical/electromagnetic processes in the brain and possible electromagnetic and quantum physical processes in components of the cytoskeleton (Craddock and Tuszynski, 2010; Craddock *et al.*, 2012; Saha *et al.*, 2012; Pothos and Busemeyer, 2013; Hameroff, 2014; Havelka *et al.*, 2014). Regarding the propagation of electromagnetic fields inside subcellular and cellular structures, mitochondria might facilitate cable-like connection as already proposed by Thar and Kühl (Thar and Kühl, 2004). This aspect could be of relevance to explain how electromagnetic fields could propagate through MNTs that connect brain cells and contain mitochondria. Additionally, there could be another type of (VT-based) neuronal cell-to-cell communication via high-frequency electromagnetic fields, i.e., in the optical wavelength range by ultra-weak photon emission. This type of cellular information transmission in the brain has already been proposed (Bókkon *et al.*, 2010; Bókkon *et al.*, 2011; Rahnama *et al.*, 2011; Salari *et al.*, 2012; Bókkon *et al.*, 2013) and initial experimental investigations conducted (Sun *et al.*, 2010; Tang and Dai, 2013, 2014). There could be also a connection between the findings in *in vitro* experiments about optical/electromagnetic coupling of cell cultures (Fels, 2009; Cifra *et al.*, 2011; Reguera, 2011; Rossi *et al.*, 2011; Kučera and Cifra, 2013; Scholkmann *et al.*, 2013; Prasad *et al.*, 2014) and electromagnetic processes in the brain. Lastly, the insight that the brain's electromagnetic field is not an epiphenomenon could possibly lead to a new understanding about the biological significance of the magnetite ( $\text{Fe}_3\text{O}_4$ ) particles found in the brain: they could function as a shield to protect the endogenous electromagnetic fields against the exogenous ones (Størmer, 2014), and/or they could be involved in the electrical and electromagnetic processes in the brain (Banaclocha *et al.*, 2010; Bókkon and Salari, 2010; Størmer *et al.*, 2011, 2013).

Taken all together, the new experimental evidences for new ways of WT-based and VT-based cell-to-cell communication open up great possibilities for future research that has the potential to deliver breakthroughs in the understanding of the biophysical processes happening in our central nervous system.

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